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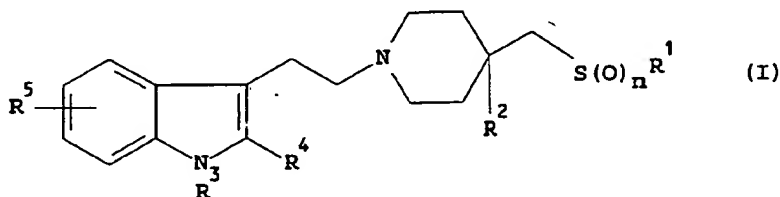
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP93/00101 (22) International Filing Date: 15 January 1993 (15.01.93) (30) Priority data: 9201179.0 21 January 1992 (21.01.92) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : COOPER, Anthony, William, James [GB/GB]; Glaxo Group Research Limited, Berkeley Avenue, Greenford, Middlesex UB6 0HE (GB). HAGAN, Russell, Michael [GB/GB]; Glaxo Group Research Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB).		(74) Agents: BREWER, Christopher, Laurence et al.; Glaxo Holdings plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.

(54) Title: PIPERIDINE DERIVATIVES



(57) Abstract

The present invention relates to the novel piperidine derivatives of formula (I) wherein R¹ represents phenyl optionally substituted by one or two C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl groups or halogen atoms; R² represents hydrogen, hydroxy or C₁₋₄alkoxy; R³ represents hydrogen or C₁₋₄alkyl; R⁴ represents hydrogen, C₁₋₄alkyl or C₁₋₄alkoxy; R⁵ represents hydrogen, a C₁₋₄alkyl, trifluoromethyl or cyano group, or a halogen atom; n represents zero, 1 or 2; and pharmaceutically acceptable salts thereof, processes for their preparation, pharmaceutical compositions containing them and their medical use. The invention also relates to the use of tachykinin antagonists, including NKA, NKB and substance P, acting at the NK₂ receptor in the treatment of anxiety disorders.

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PIPERIDINE DERIVATIVES

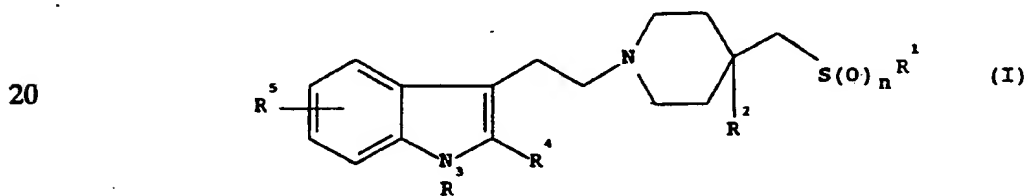
This invention relates to piperidine derivatives, to processes for their preparation, to
 5 pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to compounds which are potent and specific
 antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK₂
 receptor. The invention also relates to a novel medical use for antagonists of tachykinins
 acting at the NK₂ receptor.

10 A number of tachykinin antagonists acting at the NK₂ receptor have been described,
 however, these compounds have been peptidic in nature and are therefore generally too
 metabolically labile to serve as practical therapeutic agents in the treatment of disease.

More recently, the non-peptide NK₂ receptor antagonist SR48968
 (S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]
 15 benzamide has been reported (Advenier, C., *et. al*, C82, British Pharmacological Society
 Meeting, London, December, 1991).

The present invention provides the novel piperidine derivatives of formula (I)



wherein

R¹ represents phenyl optionally substituted by one or two C₁₋₄alkyl, C₁₋₄alkoxy,
 25 trifluoromethyl groups or halogen atoms;

R² represents hydrogen, hydroxy or C₁₋₄alkoxy;

R³ represents hydrogen or C₁₋₄alkyl;

R⁴ represents hydrogen, C₁₋₄alkyl or C₁₋₄alkoxy;

R⁵ represents hydrogen, a C₁₋₄alkyl, trifluoromethyl or cyano group, or a halogen atom;

30 n represents zero, 1 or 2;

and pharmaceutically acceptable salts thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or *p*-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

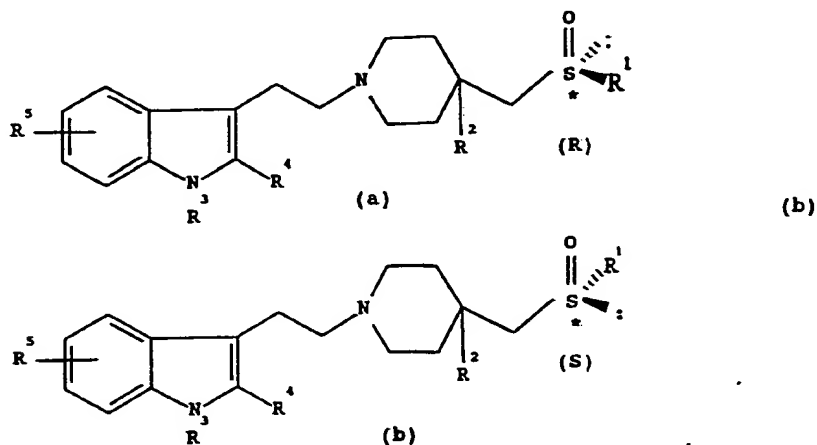
Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

References hereinafter to a compound according to the invention includes both compounds of formula (I) and their pharmaceutically acceptable acid addition salts.

It will be appreciated by those skilled in the art that when *n* represents 1 the compounds of formula (I) contain at least one chiral center (shown as * in figures (a) and (b)) and thus exist in the form of at least one pair of optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures.

For example the compounds of formula (I) may be either (R)- isomers or (S)- isomers, as represented by figures (a) and (b) respectively, or mixtures thereof.

All such isomers of the compounds of formula (I) and mixtures thereof including racemic mixtures are included within the scope of the invention.



When it appears in formula (I) and elsewhere hereinbefore and hereinafter, a C₁₋₄alkyl group may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl or 2-methylprop-2-yl. A C₁₋₄alkoxy group may be a straight chain or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or 2-methylprop-2-oxy.

Referring to the general formula (I), a halogen atom may be, for example, a fluorine, chlorine, bromine or iodine atom.

When R¹ in general formula (I) represents a substituted phenyl group the substituent(s) may be present at any available position on the phenyl ring, thus, the substituents may be present at the 2-, 3-, 4-, 5- and/or 6- (e.g. the 2- and/or 4-) position of the phenyl ring.

The substituents may be the same or different and selected from C₁₋₄alkyl (e.g. methyl), C₁₋₄alkoxy (e.g. methoxy), trifluoromethyl groups or halogen (e.g. fluorine or chlorine) atoms. Specific examples of R¹ include phenyl, 4-methylphenyl and 2-methylphenyl.

n in the compounds of formula (I) may represent zero, 1 or 2 (i.e. a sulphide, sulfoxide or sulphone respectively). n is preferably zero or 1, most preferably 1. When n is 1, the (R)-sulphoxide is preferred.

R² in the compounds of formula (I) is preferably a hydroxy group.

R³ in the compounds of formula (I) is preferably hydrogen.

R⁴ in the compounds of formula (I) is preferably hydrogen.

R⁵ in the compounds of formula (I) may represent hydrogen, C₁₋₄alkyl (e.g. methyl), a trifluoromethyl or cyano group or a halogen (e.g. fluorine) atom. When R⁵ is other than hydrogen, the substituent may be present at either the 4-, 5-, 6- or 7- (e.g. the 5-) position of the indole ring. R⁵ is preferably a halogen (e.g. fluorine) atom, more preferably a fluorine atom in the 5-position of the indole ring.

A preferred class of compounds of formula (I) is that in which R¹ represents optionally substituted phenyl (e.g. phenyl or methylphenyl, such as 2-methylphenyl or 4-methylphenyl), n represents 1, R² represents hydroxy, R³ represents hydrogen, R⁴

represents hydrogen and R⁵ represents a halogen (e.g. fluorine) atom, for example a fluorine atom in the 5-position of the indole ring.

Specific compounds according to the invention include:

- 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylsulfinyl)methyl)-4-piperidinol;
1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(((4-methyl)phenylsulfinyl)methyl)-4-piperidinol;
1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol; more specifically the (R)-enantiomers thereof, and pharmaceutically acceptable salts thereof,
and
1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylthio)methyl)-4-piperidinol;
1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylthio)methyl]-4-piperidinol;
1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfonyl)methyl]-4-piperidinol;
1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylsulfonyl)methyl)-4-piperidinol; and pharmaceutically acceptable salts thereof.

The compounds of the invention are potent and selective antagonists at NK₂ receptors both in vitro and in vivo and are therefore useful in the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor.

For example, the compounds of the invention are antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor.

Conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor include diseases associated with reversible airways obstruction, such as asthma and chronic bronchitis, and the compounds of the invention are therefore useful for the treatment of these diseases.

Compounds of the invention are also useful as analgesics for the treatment of both acute and chronic pain in particular in the treatment of traumatic pain such as

postoperative pain; menstrual pain; headaches such as migraine and cluster headache; gastrointestinal pain; neuropathic pain; and chronic inflammatory pain.

Compounds of the invention are also useful as antiinflammatory agents in particular in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease and ulcerative colitis and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of CNS disorders such as psychoses such as schizophrenia, mania, dementia or other cognitive disorders e.g. Alzheimer's disease; depression; Parkinson's disease; dependency on drugs or substances of abuse; motor disorders such as tardive dyskinesias, Huntingtons Chorea and epilepsy; and also the compounds of the invention act as myorelaxants and antispasmodics.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; and cough.

The compounds' NK₂-receptor antagonist activity has been demonstrated in vitro by their ability to antagonise the contractile effects in isolated guinea-pig trachea induced by the selective NK₂ agonist GR64349, using the method of Ireland et al in Brit.J.Pharmacol., 103, 1463-1469, (1991).

The compounds of the invention have been shown to exhibit NK₂ receptor antagonist activity in vivo by for example their ability to antagonise GR64349 induced bronchoconstriction in the anaesthetised guinea-pig using the method of Hagan et al in Neuropeptides, 19, 127-135, (1991) with the antagonist administered intravenously or intraduodenally.

The invention therefore further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Reports of the potential use of tachykinin antagonists in the treatment of anxiety have been made, for example as in EP436334, however, no evidence has been provided for this use. The use of antagonists of tachykinins acting at the NK₂ receptor in the treatment of anxiety has not previously been reported. We have now found that a further condition mediated by NK₂ receptors is anxiety.

The invention therefore provides, in an alternative or further aspect, the novel use of antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor, in the treatment of anxiety disorders.

There is also provided as a further aspect of the invention the use of antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor, in the preparation of a medicament for use in the treatment of anxiety disorders.

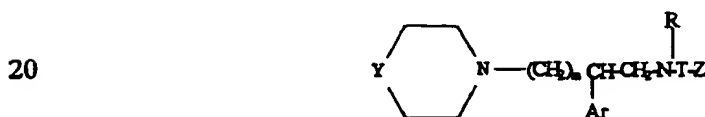
In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to anxiety disorders, comprising administration of an effective amount of an antagonist of tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor.

Anxiety disorders as mentioned hereinbefore include panic disorder, agoraphobia, social phobia, simple phobia, obsessive compulsive disorders, post traumatic stress disorder, and general anxiety disorder.

Antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK₂ receptor, have been shown to have anxiolytic activity as demonstrated by for example their ability to increase the time spent by rats in the aversive open arms of an elevated plus maze, using a method modified from Handley and Mithani in Naunyn-Schmiedeberg's Arch. Pharmacol., 327, 1-5 (1984), and by their performance in the mouse light-dark box test as described by Costall et al in Pharmacol. Biochem. and Behav., 32, 777-785 (1989).

It will be appreciated by those skilled in the art that any compound possessing NK₂ antagonist activity may be used in the treatment of anxiety disorders.

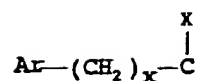
Specific antagonists of tachykinins for use in the treatment of anxiety disorders include, for example, the compounds according to the invention and those compounds generically and specifically disclosed in EP474561 and EP512901 which disclosures are incorporated herein by reference;
i.e. compounds of formula



in which

Y represents - either a group Cy-N in which Cy represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:
hydrogen, a halogen atom, a hydroxyl, a C₁-C₄ alkoxy, a C₁-C₄alkyl, a trifluoromethyl, the said substituents being identical or different; a C₃-C₇ cycloalkyl group; a pyrimidinyl group or a pyridyl group;

or a group



5 in which Ar represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

hydrogen, a halogen atom, a hydroxyl, a C₁-C₄ alkoxy, a trifluoromethyl, a C₁₋₄ alkyl, the said substituents being identical or different; a pyridyl group; a thienyl group;

x is zero or one;

10 X represents a hydroxyl, a C₁-C₄ alkoxy; a hydroxyalkyl in which the alkyl is a C₁-C₃ group; a C₁-C₄ acyloxy; a phenacyloxy; a carboxyl; a C₁-C₄ carbalkoxy; a cyano; an aminoalkylene in which the alkylene is a C₁-C₃ group; a group -N(X)₂ in which the groups X₁ independently represent hydrogen, a C₁-C₄ alkyl; a group



in which Alk represents a C₁-C₆ alkyl;

a group



in which Alk₁ is a C₁-C₃ alkylene and Alk'₁ is a C₁-C₃ alkyl; a C₁-C₄ acyl; a group -S-X₂ in which X₂ represents hydrogen or a C₁-C₄ alkyl group; or alternatively X forms a double bond with the carbon atom to which it is linked and with the adjacent carbon atom in the heterocycle;

25 m is 2 or 3;

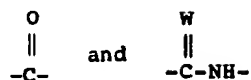
Ar' represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

hydrogen, a halogen atom, preferably a chlorine or fluorine atom, a trifluoromethyl, a C₁-C₄ alkoxy, a C₁-C₄ alkyl, the said substituents being identical or different; a thienyl; a benzotheinyl; a naphthyl; an indolyl; an indolyl N-substituted with a C₁-C₃ alkyl;

30

R represents hydrogen, a C₁-C₄ alkyl;

T represents a group selected from



5

W being an oxygen or sulphur atom, and

Z represents either hydrogen, or M or OM when T represents

10



or M when T represents a group



15

M represents a C₁-C₆ alkyl; a phenylalkyl in which the alkyl is a C₁-C₃ group, optionally substituted on the aromatic ring with a halogen, a trifluoromethyl, a C₁-C₄ alkyl, a hydroxyl, a C₁-C₄ alkoxy; a pyridyl alkyl in which the alkyl is a C₁-C₃ group, a naphthylalkyl in which the alkyl is a C₁-C₃ group, optionally substituted on the naphthyl ring system with a halogen, a trifluoromethyl, a C₁-alkyl, a hydroxyl, a C₁-C₄ alkoxy; a pyridylthioalkyl in which the alkyl is a C₁-C₃ group; a styryl; an optionally substituted mono-, di- or tricyclic aromatic or heteroaromatic group; or one of its salts with inorganic or organic acids;

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more particularly

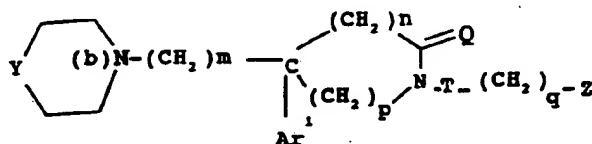
N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]

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benzamide in racemic form or in the form of the (+) or (-) enantiomers; and its salts with organic or mineral acids;

and compounds of formula

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wherein

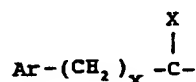
Y represents either Cy-N or Cy-CH₂-N wherein

Cy represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

- 5 a halogen atom, a hydroxyl, a C₁-C₄ alkoxy, a C₁-C₄ alkyl, a trifluoromethyl, the said substituents being identical or different; a C₃-C₇ cycloalkyl group; a pyrimidinyl group or a pyridyl group;

- or a group

10



in which Ar represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from: hydrogen, a halogen atom, a hydroxyl, a C₁-C₄ alkoxy, a trifluoromethyl, a C₁-C₄ alkyl, the said substituents being identical or different; a pyridyl group; a thienyl group;

15

x is zero or one;

X represents hydrogen, a hydroxyl, a C₁-C₄ alkoxy; a C₁-C₄ acyloxy; a carboxyl; a C₁-C₄ carbalkoxy, a cyano; a group -N-(X₁)₂ in which the groups X₁ independently represent hydrogen, a C₁-C₄ alkyl; C₁-C₄ hydroxyalkyl; C₁-C₄ acyl; or -(X₁)₂ forms, together with the nitrogen atom to which it is attached, a heterocycle selected from pyrrolidine, piperidine or morpholine; a group -S-X₂ in which X₂ represents hydrogen or a C₁-C₄ alkyl group; or alternatively X forms a double bond with the carbon atom to which it is linked and with the adjacent carbon atom in the heterocycle;

20

25 m is 2 or 3;

Ar' represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

a halogen atom, preferably a chlorine or fluorine atom, a trifluoromethyl, a C₁-C₄ alkoxy, a C₁-C₄ alkyl, the said substituents being identical or different; a thienyl; a benzothienyl; a naphthyl; an indolyl;

30

n is 0, 1, 2 or 3;

p is 1 or 2 and when p is 2, then n is 1 and Q represents two hydrogen atoms;

Q represents oxygen or two hydrogen atoms;

T represents a group selected from

5



and $-\text{CH}_2-$;

q is 0, 1, 2 or 3;

10

Z represents phenyl, unsubstituted or substituted one or more times by a halogen atom, preferably a chlorine or fluorine atom, trifluoromethyl, C_{1-4} alkyl, hydroxyl, C_{1-4} alkoxy;

naphthyl, unsubstituted or substituted one or more times by a halogen atom, trifluoromethyl, C_{1-4} alkyl, hydroxyl; pyridyl; thienyl; indolyl; quinolyl; benzothienyl;

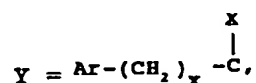
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imidazolyl; or also when T is $-\text{C}=\text{O}$, $-(\text{CH}_2)_q-$ Z may also represent a benzyl group, substituted on the $-\text{CH}-$ by hydroxyl, C_{1-4} alkoxy, C_{1-4} alkyl and optionally substituted on

the aromatic ring by a halogen atom, preferably a chlorine or fluorine atom, trifluoromethyl, C_{1-4} alkyl, hydroxyl, C_{1-4} alkoxy; an optionally substituted mono-, di- or

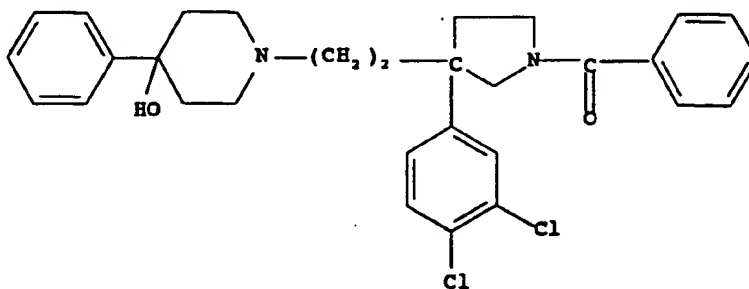
tricyclic aromatic or heteroaromatic group; or one of its salts with mineral or organic acids, or, when

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quaternary ammonium salts or piperidine N-oxide derivative at the nitrogen atom (b); more particularly

25



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and its salts with organic or mineral acids.

For use in medicine, the above mentioned tachykinin antagonists may be administered as the raw chemical but are preferably presented as pharmaceutical formulations. Suitable pharmaceutical formulations are described in the above referenced patent specifications. In addition, the compounds may be formulated as described hereinafter for the compounds of formula (I).

Compounds according to the invention may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such

as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds according to the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

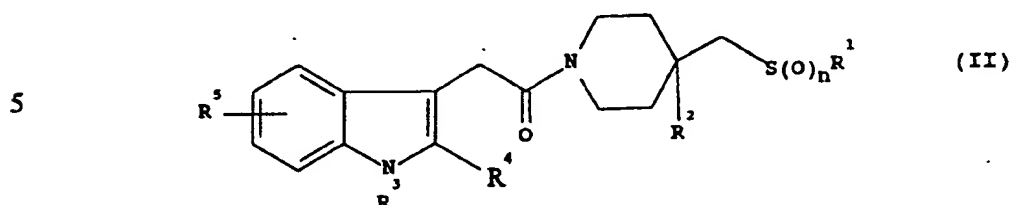
A proposed dose of the compounds of the invention is 0.001 mg/kg to about 400 mg/kg bodyweight per day. Suitable dose ranges for other tachykinin antagonists for use in anxiety are described in the above referenced patent specifications, that is to say that for use in anxiety the compounds may be used at doses appropriate for other conditions for which tachykinin antagonists are known to be useful. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

The compounds of formula (I) and other tachykinin antagonists may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate dosages will be readily appreciated by one skilled in the art.

Compounds of formula (I), and salts thereof, may be prepared by the general methods outlined hereinafter.

In the following description the groups R^1 to R^5 and n are as defined in formula (I) unless otherwise stated.

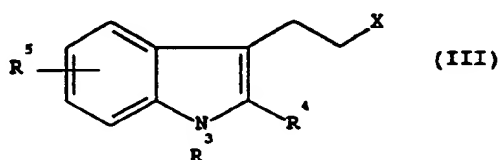
According to a first general process (A) compounds of formula (I) where n is zero or two may be prepared by reduction of appropriate tertiary amides of formula (II)



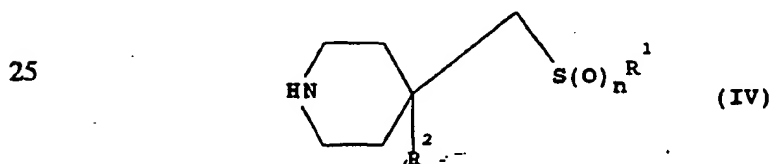
10 The reduction conveniently takes place using a suitable reducing agent, such as a hydride reducing agent, e.g. borane or lithium aluminium hydride.

Thus for example, the reduction conveniently takes place using borane-tetrahydrofuran complex in a suitable solvent such as an ether (e.g. tetrahydrofuran) and at a temperature in the range of 0-30°C.

15 According to a further general process (B) compounds of formula (I) may be prepared by reaction of a compound of formula (III)



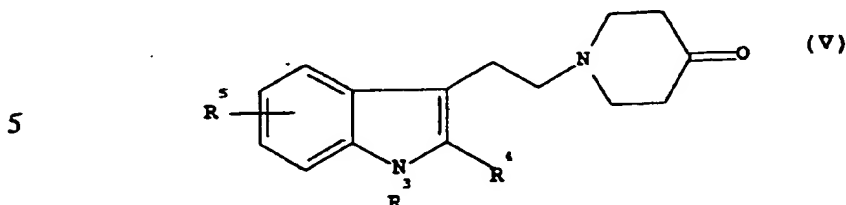
20 (wherein X represents a suitable leaving atom or a group such as a halogen (e.g. bromine or iodine) atom, or a sulphonyloxy (e.g. p-toluenesulphonyloxy) group with a compound of formula (IV)



30 The reaction conveniently takes place in a suitable solvent such as an amide (e.g. dimethylformamide) or a chlorinated hydrocarbon at a temperature in the range of 0-30°C, preferably in the presence of a base (e.g. triethylamine or potassium carbonate).

16

According to a further general process (C) compounds of formula (I) where n is 1 or two and R² is hydroxy may be prepared by reaction of a compound of formula (V)



with a compound of formula (VI)

10



after deprotonation with a strong base such as lithium bis(trimethylsilyl) amide or lithium diisopropylamide.

15

The reaction conveniently takes place in a suitable solvent such as an ether (e.g. tetrahydrofuran) at a temperature ranging from -70 to +30°C (e.g. -70°C).

According to a further general process (D) a compound of formula (I) may be converted into another compound of formula (I) using conventional techniques.

Such conventional techniques include for example oxidation or reduction.

20

For example compounds of formula (I) where n is 1 may be prepared by oxidation of compounds of formula (I) where n is zero using conventional oxidising agents, for example using a periodate oxidising agent such as sodium periodate.

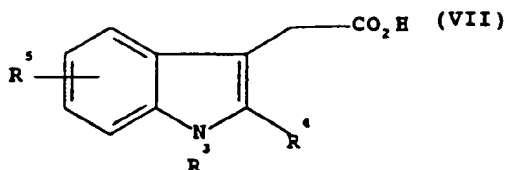
Oxidation conveniently takes place in a suitable solvent such as an alcohol (e.g. aqueous methanol) at ambient temperature.

25

Reduction of compounds of formula (I) where n is 1 to compounds of formula (I) where n is zero may be effected using a hydride reducing agent, such as borane, under the conditions described above for process (A).

30

Compounds of formula (II) may be prepared by reacting an acid of formula (VII)



or an acylating agent corresponding thereto, with a piperidine of formula (IV) as defined hereinbefore.

Thus, for example, acylation may be effected by reacting the free acid (VII) with the compound (IV) in the presence of a condensing agent, for example a carbodiimide such as N, N'-dicyclohexylcarbodiimide.

The reaction conveniently takes place in the presence of a suitable solvent such as an amide (e.g. dimethylformamide) or a chlorinated hydrocarbon at a temperature in the range of 0-30°C.

The acids of formula (VII) are either known or may be prepared by methods known for the preparation of known compounds.

Compounds of formula (IV) may be prepared by deprotection of the corresponding N-carbamate derivatives, for example the N-benzyloxycarbonyl or N-t-butyloxycarbonyl derivatives. For example N-benzyloxycarbonyl groups may be removed using catalytic hydrogenation e.g. hydrogenation in the presence of palladium on carbon. N-t-butyloxycarbonyl groups may be removed using acid catalysed hydrolysis e.g. using a solution of hydrochloric acid in dioxan or p-toluenesulphonic acid in acetonitrile.

The N-carbamate derivatives of the compounds of formula (IV) where n is zero and R² is hydroxy may be prepared by reacting the corresponding N-protected piperidine 4-epoxide with a thiol of formula (VIII)



in the presence of a base such as sodium hydride or triethylamine, conveniently in a solvent such as an amide (e.g. dimethylformamide).

The carbamate derivatives of the compounds of formula (IV) where n is one or two may be prepared by oxidation of the corresponding compounds where n is zero (or one) using a suitable oxidising agent.

Thus compounds where n is one may be prepared by oxidising compounds where n is zero using a periodate oxidising agent such as sodium periodate, or one equivalent of a peracid oxidising agent.

Compounds where n is two may be prepared by oxidising compounds where n is zero or one with an oxidising agent such as a peracid (e.g. *m*-chloroperoxybenzoic acid).

The N-carbamate piperidine 4-epoxides may be prepared by reacting the corresponding 4-oxo-piperidine with the ylid derived from trimethyl sulfoxonium iodide.

Alternatively, the N-carbamate derivatives of the compounds of formula (IV) where n is one or two and R^2 is hydroxy may be prepared by reacting N-carbamate 4-oxo-piperidine with a compound of formula (VI) after deprotonation with a strong base such as lithium bis(trimethylsilyl) amide or lithium diisopropylamide.

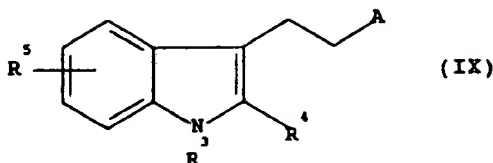
The reaction conveniently takes place in a suitable solvent such as an ether (e.g. tetrahydrofuran) at a temperature ranging from -70 to 30°C (e.g. -30°C).

The N-carbamate derivatives of the compounds of formula (IV) where n is zero and R^2 is hydrogen may be prepared by reacting the corresponding N-protected 4-bromomethyl piperidine with the thiol of formula (VIII).

The compounds may be oxidised to give further values of n as described above.

The N-carbamate derivatives of the compounds of formula (IV) where R^2 is C_{1-4} alkoxy may be prepared by reacting the corresponding N-protected compounds of formula (IV) where R^2 is hydroxy with a C_{1-4} alkyl iodide in the presence of a base such as potassium hydroxide, conveniently in a solvent such as a polar aprotic solvent (e.g. dimethylsulfoxide).

Compounds of formula (V) may be prepared by reacting a compound of formula (IX)



(where A represents either (a) a halogen atom (e.g. bromine) or (b) -NH_2) with either (a) 4-oxo-piperidine or (b) a simple alkyl quaternary salt of 4-oxo-piperidine (e.g. 1,1-dimethyl-4-oxopiperidinium iodide).

The reaction conventionally takes place in the presence of a suitable base such as (a) triethylamine or (b) potassium carbonate, in a suitable solvent such as (a) an amide such as dimethylformamide or (b) an aqueous alcohol such as ethanol.

When a specific stereoisomer of a compound of formula (I) is required this may be prepared, for example, by resolution of the appropriate enantiomeric mixture of the compounds of formula (I) using conventional methods (see for example *Stereochemistry of Carbon Compounds* by E.L. Eliel (McGraw Hill 1962)).

Thus, where individual enantiomers of the compounds of formula (I) are required, these may be obtained from the enantiomeric mixtures of compounds of formula (I) by chromatography using a chiral column. Alternatively, enantiomeric mixtures of compounds of formula (I) may be separated for example using fractional crystallisation. Enantiomeric mixtures of compounds of formula (I) may be separated by forming a salt with a suitable chiral acid. (e.g. tartaric acid).

Individual enantiomers of the compounds of formula (I) may also be obtained from intermediates having the required chirality. Such intermediates may be obtained on resolution of their enantiomeric mixtures where the intermediates concerned contain a chiral centre. For example, enantiomeric mixtures of Intermediates of formula (IV) where n is one may be separated by forming a salt with a suitable chiral acid (e.g. tartaric acid). Alternatively, individual enantiomers may be obtained by asymmetric synthesis.

Thus, using general process (C) described hereinbefore, compounds of formula (I) where n is one may be prepared having a specific configuration as represented by figures (a) and (b) described hereinbefore.

Thus compounds of formula (V) may be reacted with a chiral sulfoxide of formula
5 (VIa) or (VIb)



10 under the conditions as described above for process (C).

It will be appreciated that the above described methods may additionally be combined in any suitable sequence to obtain the compounds of formula (I) and the intermediates thereof.

15 Compounds of formulae (II) and (IV) are novel and form a further feature of the invention.

The invention is further illustrated by the following, non-limiting, Intermediates and Examples. Organic extracts were dried, where indicated, over magnesium sulphate. Temperatures are in °C. CD refers to circular dichroism spectroscopy.

20 Intermediate 1

2-(5-Fluoro-1H-indol-3-yl)-1-[4-oxo-1-piperidinyl]ethanone

A solution of 2-(5-fluoro-1H-indol-3-yl) ethanoic acid (2.0g) in dimethylformamide (10ml) was treated with dicyclohexylcarbodiimide (2.13g) and 1-hydroxybenzotriazole (1.4g). After stirring for fifteen minutes the suspension was treated with 4-piperidone
25 hydrochloride (2.30g) and triethylamine (2.23ml). The reaction was stirred at 20° for 24 hours, then diluted with ethyl acetate (40ml), filtered, and the solids washed with ethyl acetate. The combined organics were washed with water (100ml), saturated aqueous sodium bicarbonate (100ml) and brine (100ml), dried and evaporated in vacuo to give the title compound (2.59g). ¹H NMR (250MHz, DMSO-D₆) δ, 11.05 (1H, s), 7.25-7.4

(3H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 3.7-3.9 (6H,m,complex), 2.2-2.4 (4H,m,complex) ppm.

Intermediate 2

5 2-(5-Fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-[(phenylsulfinyl)methyl]-1-piperidinyl]ethanone

To a solution of lithium bis(trimethylsilyl) amide (4ml; 1M in tetrahydrofuran) was added dropwise at -70°, a solution of methylphenylsulfoxide (561mg) in tetrahydrofuran (4ml). After stirring for 5mins the reaction was treated with a solution of 2-(5-
10 fluoro-1H-indol-3-yl)-1-(4-oxo-1-piperidinyl)ethanone (549mg) in tetrahydrofuran (10ml). After 10mins the reaction was quenched with saturated aqueous ammonium chloride (5ml), diluted with water (20ml) and extracted with ethyl acetate (50ml). The organic phase was washed with brine (30ml), dried and the solvent removed in vacuo to give a brown oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (50:1-19:1) the appropriate fractions being bulked and
15 the solvent removed in vacuo to give the title compound (450mg) as a white foam. ¹H NMR (250MHz,DMSO-D6) δ, 11.05 (1H,s), 7.5-7.7 (5H,m,complex), 7.25-7.35 (3H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 5.7 (1H,d J=4Hz), 3.95-4.1 (1H,m,complex), 3.7-3.85 (3H,m,complex), 3.25-3.45 (m,obscured by solvent), 2.95-3.1
20 (1H,m,complex), 2.75-2.95 (2H,m,complex), 1.45- 1.8 (3H,m,complex) ppm.

Intermediate 3

2-(5-Fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-((2-methyl) phenylsulfinyl) methyl]-1-piperidinyl]ethanone

25 To a solution of lithium bis(trimethylsilyl) amide (14ml; 1M in tetrahydrofuran) was added dropwise, at -70°, a solution of methyl (2-methylphenyl)sulfoxide (2.0g) in tetrahydrofuran (10ml). After stirring for 5mins the reaction was treated with a solution of 2-(5-fluoro-1H-indol-3-yl)-1-(4-oxo-1-piperidinyl)ethanone (1.65g) in
tetrahydrofuran (30ml). After 20mins the reaction was quenched with saturated aqueous
30 ammonium chloride (5ml), diluted with water (20ml) and extracted with ethyl acetate

(2x50ml). The combined organic phases were washed with brine (50ml), dried and the solvent removed in vacuo to give a brown oil. This was purified by column chromatography on silica (Merck 9385) eluting with chloroform:methanol (50:1- 30:1) the appropriate fractions being bulked and the solvent removed in vacuo to give the title compound (850mg). ¹H NMR (250MHz,DMSO-D6) δ , 11.0 (1H,s), 7.7-7.85 (1H,m,complex), 7.25-7.55 (6H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 5.15 (1H,m), 4.0-4.15 (1H,m,complex), 3.7-3.85 (3H,m,complex), 3.25- 3.45 (m,obscured by solvent), 3.18 (1H,d J=5Hz), 2.95-3.1 (1H,m,complex), 2.65-2.85 (2H,m,complex), 2.3 (3H,s), 1.4-1.85 (4H,m,complex) ppm.

Intermediate 4

4-Hydroxy-4-(((2-methyl)phenylthio)methyl)-1-piperidine carboxylic acid, phenyl methyl ester

A solution of α -thiocresol (248mg) in dimethylformamide (2ml) was treated with sodium hydride (80mg; 60% dispersion in mineral oils) and when effervescence had ceased with 1-oxa-6-azaspiro [2.5]octane- 6-carboxylic acid, phenylmethyl ester (494mg). The reaction was maintained at 20° for 3 days, diluted with ethyl acetate (50ml), washed with water (50ml), saturated aqueous sodium bicarbonate (50ml) and brine (50ml), dried and the solvent removed in vacuo to give the title compound as a viscous gum (740mg). ¹H NMR (250MHz, CDCl₃) δ 7.3-7.45 (6H, m, complex), 7.1-7.25 (3H, m, complex), 5.1 (2H, s), 3.85-4.1 (2H, m, complex), 3.1-3.3 (2H, m, complex), 3.05 (2H, s), 2.4 (3H, s), 2.2 (1H, s), 1.4-1.75 (4H, m, complex) ppm.

Intermediate 5

4-Hydroxy-4-(((2-methyl)phenylsulfonyl)methyl)-1-piperidine carboxylic acid, phenyl methyl ester

A solution of 4-hydroxy-4-(((2-methyl)phenylthio)methyl)-1- piperidinecarboxylic acid, phenylmethyl ester (590mg) in chloroform (5ml) was treated with m-chloroperbenzoic acid (760mg; 80%) and stirred at 20° for 24h. The white suspension was diluted with dichloromethane (60ml), washed with aqueous sodium metabisulfite (40ml), saturated

aqueous sodium bicarbonate (2x40ml), dried and the solvent removed in vacuo to give a waxy oil. This was purified by column chromatography on silica (Merck 7734) eluting with cyclohexane:ethyl acetate (9:1 -1:2) the appropriate fractions being bulked and the solvent removed in vacuo to yield the title compound (536mg) as a gum. IR (CHBr₃) values include 3500, 1686, 1472, 1435, 1053, 755 cm⁻¹.

Intermediate 6

4-(((2-Methyl)phenylsulfonyl)methyl)-4-piperidinol

A solution of 4-hydroxy-4-(((2-methyl)phenylsulfonyl)methyl)-1- piperidine carboxylic acid, phenylmethyl ester (480mg) in ethanol (10ml) was hydrogenated over 5% palladium on carbon (450mg) for 18h. The catalyst was removed by filtration and then solvent removed in vacuo. The residue was partitioned between diethyl ether (50ml) and 0.5N hydrochloric acid (30ml), the aqueous layer basified with sodium hydroxide solution, and extracted with chloroform (3x25ml), dried and evaporated to give the title compound (191mg). ¹H NMR (250MHz, CDCl₃) δ 8.02 (1H, m, complex), 7.55 (1H, m, complex), 7.3-7.45 (2H, m, complex), 3.3 (2H, s), 2.95-3.15 (2H, m, complex), 2.75-2.9 (2H, m, complex), 2.7 (3H, s), 1.6-2.0 (4H, m, complex) ppm.

Intermediate 7

2-(5-Fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-(((2-methyl)phenylsulfonyl)methyl)-1-piperidinyl] ethanone

A solution of 4-(((2-methyl)phenylsulfonyl)methyl)-4-piperidinol (137mg) and 2-(5-fluoro-1H-indol-3-yl)ethanoic acid (135mg) in dry dimethylformamide (2ml) was treated with dicyclohexylcarbodiimide (144mg) and 1-hydroxybenzotriazole (95mg). After stirring for 16 hours the reaction was diluted with ethyl acetate (40ml) filtered, and the solid washed with ethyl acetate. The organic solution was washed with 2N hydrochloric acid (30ml), saturated aqueous sodium bicarbonate solution (30ml) and saturated brine (30ml), dried and the solvent removed in vacuo to give an opaque oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (19:1) the appropriate fractions being bulked and the solvent

removed in vacuo to give the title compound (188mg) as an off-white foam. ¹H NMR (250MHz, DMSO-D₆) δ 11.0 (1H, s), 7.85 (1H, m), 7.6 (1H, m), 7.2-7.5 (5H, m, complex), 6.9 (1H, t 9Hz, d 2Hz), 4.82 (1H, s), 4.0-4.1 (1H, m), 3.6-3.8 (3H, m, complex), 3.4 (2H, s), 3.2-3.4 (m, obscured by solvent), 2.75-3.0 (1H, m, complex), 2.62 (3H, s), 1.5-1.7 (4H, m, complex) ppm.

Intermediate 8

1-Oxa-6-azaspiro[2.5]octane-6-carboxylic acid,1,1-dimethylethyl ester

A suspension of trimethylsulfoxonium iodide (35.2g) in dimethyl sulfoxide (200ml) was treated portionwise, under nitrogen, with sodium hydride (6.2g; 60% dispersion in mineral oil). When effervescence had ceased, this was treated with a solution of 1-piperidine-carboxylic acid, 4-oxo,1,1-dimethylethyl ester (27.2g) in dimethyl sulfoxide and the resulting solution stirred at 20° for 1h. The reaction was quenched with ice/water (500ml), extracted with diethyl ether (2x500ml), the combined organics washed with water (2x300ml) and saturated brine (200ml), dried and the solvent removed in vacuo to give the title compound as a white solid (26.7g). ¹H NMR (250MHz, CDCl₃) δ 3.65-3.8 (2H, m, complex), 3.35- 3.5 (2H, m, complex), 2.7 (2H, s), 1.7-1.9 (2H, m, complex), 1.35- 1.55 (2H, m, complex), 1.48 (9H, s) ppm.

Intermediate 9

4-Hydroxy-4-[(2-methyl)phenylthio)methyl]-1-piperidinecarboxylic acid,1,1-dimethylethyl ester

A solution of 1-oxa-6-azaspiro[2.5]octane-6-carboxylic acid,1,1- dimethyl ester (853mg) in dimethylformamide (5ml) was treated with σ-thiocresol (497mg) and triethylamine (424mg), and the resulting solution stirred at 20° for 16 hours. The reaction was diluted with ethyl acetate (50ml) and washed with 2N hydrochloric acid (40ml), saturated aqueous sodium bicarbonate solution (40ml) and brine (40ml), dried and the solvent removed in vacuo to give a viscous oil. This was purified by column chromatography on silica (Merck 7734) eluting with cyclohexane:ethyl acetate (4:1), the appropriate fractions were bulked and the solvent removed in vacuo to give the title compound

(1.18g). ¹H NMR (250MHz, CDCl₃) δ 7.4 (1H, m), 7.05-7.25 (3H, m, complex), 3.65-3.95 (2H, m, complex), 3.05-3.25 (3H, m, complex), 2.4 (3H, s), 1.4- 1.75 (4H, m, complex), 1.46 (9H, s) ppm.

5 Intermediate 10

4-(((2-Methyl)phenylthio)methyl)-4-piperidinol, hydrochloride salt

4-Hydroxy-4-(((2-methyl)phenylthio)methyl)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (160mg) was dissolved in 4M hydrochloric acid in dioxan (10ml) and stirred at 20°. After 4 hours the solvent was removed in vacuo to give the
10 title compound (140mg, contains solvent). ¹H NMR (250MHz, DMSO-D₆) δ 8.9 (1H, m, broad), 8.6 (1H, s, broad), 7.37 (1H, d J=7.5Hz), 7.0- 7.25 (3H, m, complex), 5.1-5.3 (1H, m, broad), 2.9-3.2 (6H, m, complex), 2.3 (3H, s), 1.6-1.9 (4H, m, complex) ppm.

Intermediate 11

15 2-(5-Fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-(((2-methyl)phenylthio)methyl)-1-piperidinyl]-ethanone

A stirred solution of 4-(((2-methyl)phenylthio)methyl)-4-piperidinol hydrochloride salt (657mg) in dimethylformamide (5ml) was treated with triethylamine (267mg), 2-(5-fluoro-1H-indol-3-yl)ethanoic acid (464mg), dicyclohexylcarbodiimide (495mg)
20 and 1-hydroxybenzotriazole (324mg). After stirring for 3 days the reaction was diluted with ethyl acetate (150ml), filtered and the organic solution washed with 10% aqueous citric acid solution (100ml), saturated aqueous sodium bicarbonate solution (100ml) and brine (50ml). The solution was dried and the solvent removed in vacuo to give a viscous gum. This was purified by column chromatography on silica (Merck 9385) eluting with
25 chloroform:methanol (49:1) the appropriate fractions were bulked and the solvent removed in vacuo to give the title compound (420mg). ¹H NMR (250MHz, DMSO-D₆) δ 11.0 (1H, s), 7.0- 7.35 (6H, m, complex), 6.9 (1H, t J=9Hz, d J=2Hz), 4.8 (1H, s), 4.05-4.2 (1H, m), 3.7-3.85 (3H, m, complex), 3.2-3.4 (m, complex,

obscured by solvent), 2.8-3.1 (3H, m, complex), 2.25 (3H, s), 1.3- 1.6 (4H, m, complex) ppm.

Intermediate 12

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-oxo-piperidine

a) A solution of 4-piperidone monohydrate hydrochloride (2.2g) and 2-(5-fluoro-1H-indol-3-yl)ethyl bromide (2.47g) in dimethylformamide (8ml) was treated with potassium carbonate (3.52g) and the suspension stirred at 20° for 72h. The reaction mixture was diluted with water (80ml) and ethyl acetate (150ml). The phases were separated and the organic phase washed with water (2x60ml). The organic extract was dried and the solvent was removed in vacuo. The residue was purified by column chromatography on silica (Merck 9385) eluting with methanol:ethyl acetate (1:19 to 1:9) the appropriate fractions were bulked to give the title compound (2.12g). IR (CHBr₃) values include 3466, 2812, 1713, 1484, 1454, 1352, 938, 795cm⁻¹.

b) A solution of 5-fluorotryptamine hydrochloride (4.00g) in ethanol (80ml) and water (40ml) was treated with potassium carbonate (8.4g). The solution was stirred at reflux under nitrogen whilst a solution of 1,1-dimethyl-4-oxo piperidinium iodide (5.3g) in water (40ml) was added dropwise over a period of 30mins. After stirring at reflux for a further 2h, the ethanol was removed in vacuo and residue diluted with dichloromethane (50ml). The phases were separated and the aqueous phase extracted with dichloromethane (50ml). The combined organic phases were washed with brine (30ml), dried and the solvent removed in vacuo to give a red oil. This was purified by column chromatography on silica (Merck 9385) eluting with chloroform:methanol (20:1), the appropriate fractions were bulked and the solvent removed in vacuo to give the title compound as an off-white solid (3.9g). IR (CHBr₃) values include 3466, 2812, 1713, 1484, 1454, 1352, 938, 795cm⁻¹.

Example 1

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylthio)methyl]-4-piperidinol

A solution of 2-(5-fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-[(phenylsulfinyl)methyl]-1-piperidinyl]ethanone (342mg) in tetrahydrofuran (5ml) was treated with borane-tetrahydrofuran complex (5ml; 1.0M in tetrahydrofuran) and stirred at 20° for 2h. The reaction was quenched with methanol (20ml) and maintained at reflux for 3h. The solvents were removed in vacuo to give an opaque oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (19:1) the appropriate fractions were bulked and the solvent removed in vacuo to give the title compound (175mg) as a white solid. ¹H NMR (250MHz,DMSO-D6) δ, 10.85 (1H,s), 7.1-7.4 (8H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 4.6 (1H,s), 3.1 (2H,s), 2.3-2.9 (m,obscured by solvent), 1.5-1.8 (4H,m,complex) ppm.

Example 2

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylthio)methyl]-4-piperidinol, methane sulfonic acid salt

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylthio)methyl]-4-piperidinol (76mg) was dissolved in tetrahydrofuran (5ml) and treated with methane sulfonic acid (14.3μl) and then diluted with diethyl ether. The resulting solid was collected by filtration and dried in vacuo to give the title compound (60mg). IR (Nujol) values include 1460, 1153, 1039cm⁻¹. Analysis calculated for C₂₂H₂₅FN₂OS. CH₃SO₃H, 0.25H₂O: C,57.00; H,6.08; N,5.78; S,13.22; H₂O,0.93; Found C,56.66; H,6.14; N,5.88; S,13.31; H₂O,0.6%.

Example 3

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylthio)methyl)-4-piperidinol

A solution of 2-(5-fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-(((2-methyl)phenylsulfinyl)methyl)-1-piperidinyl]ethanone (800mg) in tetrahydrofuran (4ml) was treated with borane-tetrahydrofuran complex (8ml;1.0M in tetrahydrofuran) and stirred at 20° for 5 mins. The reaction was quenched with methanol (15ml) and maintained at reflux for 2h. The solvents were removed in vacuo to give an opaque oil. This was purified by column chromatography on silica (Merck 9385) eluting with chloroform:methanol (30:1) and the

appropriate fractions were bulked and the solvent removed in vacuo to give the title compound (289mg). ¹H NMR (250MHz,DMSO-D6) δ, 10.85 (1H,s), 7.0-7.35 (7H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 4.58 (1H,s), 3.15 (2H,d J=5Hz), 3.05 (2H,s), 2.7-2.85 (2H,m,complex), 2.3- 2.7(m,complex,obscured by solvent), 2.2 (3H,s),
5 1.5-1.75 (4H,m,complex)ppm.

Example 4

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl) phenylsulfinyl)methyl)-4-piperidinol
A solution of 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-(((2- methyl)phenylthio) methyl)-4-
10 piperidinol (75mg) in methanol (5ml) was treated with sodium periodate (127mg) in water (5ml). After stirring for 30mins the methanol was removed in vacuo, the residue partitioned between ethyl acetate (50ml) and water (50ml), the organic phase washed with brine (30ml), dried and the solvent removed in vacuo. The material obtained was bulked with a second reaction (200mg scale), and purified by column chromatography
15 on silica (Merck 9385) eluting with chloroform:methanol (9:1) the appropriate fractions being bulked and the solvent removed in vacuo to give the title compound (120mg) as a white solid. ¹H NMR (250MHz,DMSO-D6) δ, 10.9 (1H,s), 7.8 (1H,m), 7.35-7.55 (2H,m,complex), 7.2-7.35 (7H,m,complex), 6.9 (1H,t J=9Hz,d J=2Hz), 4.95 (1H,s), 2.35-2.9 (m,complex,obscured by solvent), 2.32 (3H,s), 1.6-1.9 (4H,m,complex) ppm.
20

Example 5

(S)-1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((4-methyl)phenyl sulfinyl)methyl)-4-piperidinol, methane sulfonic acid salt
A solution of lithium bis(trimethylsilyl)amide (2ml; 1M in tetrahydrofuran) at -70° was
25 treated with a solution of S(-)- methyl(4-methyl)phenyl sulfoxide (308mg). in tetrahydrofuran (2ml). After stirring for 10 mins the reaction was treated with a solution of 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-piperidone (130mg) in tetrahydrofuran (1ml). The mixture was warmed to 20°C. After stirring for 45 mins the reaction was quenched with water (20ml) and extracted with ethyl acetate (20ml). The organic phase was
30 washed with brine (20ml), dried and the solvent removed in vacuo to give a clear gum.

This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (15:1) the appropriate fractions were bulked and the solvent removed in vacuo to give a clear gum. This was redissolved in tetrahydrofuran (4ml) and treated with methane sulfonic acid (33 μ l), diluted with diethyl ether to give an off-white solid. This was collected by filtration to give the title compound (171mg). IR (Nujol) values include 3282, 1489, 1461, 1212, 1169, 1042 cm^{-1} . ^1H NMR (250MHz, DMSO-D₆) δ 11.08 (1H, s), 9.1-9.4 (1H, broad), 7.3-7.7 (7H, complex), 6.95 (1H, t, $J=9\text{Hz}$, d $J=2\text{Hz}$), 5.55 (1H, s, broad), 2.7-3.65 (m, complex, obscured by solvent), 2.4 (3H, s), 2.32 (3H, s), 1.7-2.3 (4H, m, complex) ppm. CD λ max (H_2O) 203nm ($\Delta\epsilon 16.28$), 217 nm ($\Delta\epsilon 20.62$), 241nm ($\Delta\epsilon -19.62$).

Example 6

(R)- 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[[4- methyl)phenylsulfinyl) methyl]-4- piperidinol, methane sulfonic acid salt

A solution of lithium bis(trimethylsilyl)amide (2ml;1M in tetrahydrofuran) at -70° was treated with a solution of R(+)- methyl(4-methyl)phenylsulfoxide (308mg) in tetrahydrofuran (1ml). After stirring for 5 mins the reaction was treated with a solution of 1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-piperidone (130mg) in tetrahydrofuran (1ml). The mixture was warmed to 20°C . After stirring for 30 mins the reaction was quenched with water (20ml) and extracted with ethyl acetate (40ml). The organic phase was washed with brine (20ml), dried and the solvent removed in vacuo to give a clear gum. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (9:1) the appropriate fractions were bulked and the solvent removed in vacuo to give a clear oil. This was redissolved in tetrahydrofuran (4ml) and treated with methane sulfonic acid (25 μ l), diluted with diethyl ether to give an off-white solid. This was collected by filtration to give the title compound (142mg). IR (Nujol) values include 3261, 1489, 1461, 1211, 1169, 1042 cm^{-1} . ^1H NMR (250MHz, DMSO-D₆) δ 11.08 (1H, s), 9.1-9.3 (1H, broad), 7.3-7.7 (7H, m, complex), 6.95 (1H, t, $J=9\text{Hz}$, d $J=2\text{Hz}$), 5.55 (1H, s, broad), 2.7-3.65 (m, complex, obscured by solvent), 2.4

(3H, s), 2.32 (3H, s), 1.7-2.3 (4H, m, complex) ppm. $CD\lambda_{max}$ (H_2O) 201nm ($\Delta\epsilon$ -18.23), 219 nm ($\Delta\epsilon$ -20.88), 241nm ($\Delta\epsilon$ -18.85).

Example 7

5 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfonyl)methyl]-4-piperidinol, methane sulfonic acid salt

A solution of lithium bis(trimethylsilyl)amide (2ml; 1M in tetrahydrofuran) at -70° was treated with a solution of methyl phenyl sulfone (312mg) in tetrahydrofuran (2ml). After stirring for 5 mins the reaction was treated with a solution of 1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-piperidone (130mg) in tetrahydrofuran (1ml). The mixture was warmed to $20^\circ C$. After stirring for 2h the reaction was quenched with water (30ml) and extracted with ethyl acetate (50ml). The organic phase was washed with brine (30ml), dried and the solvent removed in vacuo to give an opaque oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (19:1
15 9:1) the appropriate fractions were bulked and the solvent removed in vacuo to give a white foam. This was redissolved in tetrahydrofuran (4ml) and treated with methane sulfonic acid (36 μ l), diluted with diethyl ether to give an off- white solid. This was collected by filtration to give the title compound (204mg). IR (Nujol) values include 3290, 1461, 1448, 1153, 1150, 1041 cm^{-1} . Analysis calculated for $C_{22}H_{23}FN_2O_3S \cdot CH_4O_3S \cdot 1.1H_2O$: C, 51.88; H, 5.91; N, 5.26; S, 12.04; H_2O , 3.72. Found C, 51.78; H, 5.78; N, 4.94; S, 11.60; H_2O , 3.5%.

Example 8

25 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[[[(2-methyl)phenylsulfonyl] methyl]-4-piperidinol, hydrochloride salt

A solution of 2-(5-fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-[[[(2-methyl)phenylsulfonyl] methyl]-1-piperidinyl]ethanone (150mg) in tetrahydrofuran (5ml) was treated with borane-tetrahydrofuran complex (2ml; 1M in tetrahydrofuran) and stirred at 20° for 3 hours. The reaction was quenched with methanol (10ml) and maintained at reflux for 4
30 hours. The solvents were removed in vacuo to give an opaque oil. This was purified

A solution of 2-(5-fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-(((2-methyl)phenylsulfonyl)methyl)-1-piperidinyl]ethanone (150mg) in tetrahydrofuran (5ml) was treated with borane-tetrahydrofuran complex (2ml; 1M in tetrahydrofuran) and stirred at 20° for 3 hours. The reaction was quenched with methanol (10ml) and maintained at reflux for 4 hours. The solvents were removed in vacuo to give an opaque oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (49:1 19:1), the appropriate fractions were bulked and the solvent removed in vacuo to give an opaque oil. This was redissolved in ethyl acetate (5ml) and treated with a solution of hydrogen chloride in diethyl ether. The solvent was removed in vacuo to give the title compound (140mg) as a white solid. ¹H NMR (250MHz, DMSO-D₆) δ 11.1 (1H, s), 9.6-9.8 (1H, s, broad), 7.85-7.95 (1H, m, complex), 7.55-7.68 (1H, m, complex), 7.25-7.55 (5H, m, complex), 6.95 (1H, t J=9Hz, d J=2Hz), 5.3 (1H, s), 3.0-3.6 (m, complex, obscured by solvent), 2.7 (3H, s), 1.9-2.3 (4H, m, complex) ppm. High resolution FABMS calcd. 431.1804, found 431.1785.

Example 9

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylthio) methyl)-4-piperidinol hydrochloride salt

A solution of 2-(5-fluoro-1H-indol-3-yl)-1-[4-hydroxy-4-(((2-methyl)phenylthio)methyl)-1-piperidinyl]ethanone (140mg) in tetrahydrofuran (3ml) was treated with borane-tetrahydrofuran complex (2ml; 1M in tetrahydrofuran) and stirred at 20° for 2h. The reaction was quenched with methanol (20ml) and maintained at reflux for 3 hours. The solvents were removed in vacuo and the residue purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (50:1 9:1). The appropriate fractions were bulked and the solvent removed in vacuo to give a viscous gum. This was redissolved in tetrahydrofuran (5ml), treated with a solution of hydrogen chloride in diethyl ether (2ml; 1M) and the solvent removed in vacuo. The residue was suspended in diethyl ether and filtered to give the title compound (73mg) as an off-white solid. IR (Nujol) values include 3230, 1457, 1380 cm⁻¹. ¹H NMR (250MHz, DMSO-D₆) δ 11.1

(1H, s), 9.8-10.0 (1H, s, broad), 7.3-7.5 (4H, m, complex), 7.05-7.25 (3H, m, complex), 6.93 (1H, t J=9Hz, d J=2Hz), 5.2 (1H, s), 3.0-3.55 (m, complex, obscured by solvent), 2.32 (3H, s), 1.75-2.05 (4H, m, complex) ppm.

5 Example 10

(R)-1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol, methane sulfonic acid salt

A solution of lithium bis(trimethylsilyl)amide (12ml; 1M in tetrahydrofuran) in tetrahydrofuran (10ml) at -70°C was treated with a solution of (R)-methylphenyl
10 sulfoxide (1.65g) in tetrahydrofuran (10ml). After stirring for 10mins, the reaction was treated with a solution of 1-[5-fluoro-1H-indol-3-yl]ethyl-4-piperidone (1.04g) in tetrahydrofuran (10ml). The mixture was allowed to warm to 20°C. After stirring for 1h the reaction was quenched with water (80ml) and extracted with ethyl acetate (2x100ml). The organic phase was dried and the solvent removed in vacuo to give a yellow oil. This
15 was purified by column chromatography on silica (Merck 9385) eluting with chloroform:methanol (15:1), the appropriate fractions were bulked and the solvent removed in vacuo to give a white foam. This was redissolved in dry tetrahydrofuran (60ml) and treated with methane sulfonic acid (1.1mol equivalents), diluted with diethyl ether (350ml) to give a white solid. This was collected by filtration to give the title
20 compound (1.21g). IR (Nujol) values include 2978, 1468, 1453, 1377, 1212, 1167, 1157, 1040, 1018cm⁻¹. ¹H NMR (250MHz, DMSO-D₆) δ, 11.08 (1H, s), 9.2 (1H, s), 7.5-7.72 (5H, m, complex), 7.3-7.45 (3H, m, complex), 6.95 (1H, t J=9Hz, d J=2Hz), 5.6 (1H, broad), 2.8-3.7 (m, complex, obscured by solvent), 2.35 (3H, s), 1.7-2.3 (5H, m, complex) ppm. CD λ_{max} (H₂O) 202nm (Δε-17.45), 214 nm (Δε-22.26), 238nm (Δε 18.52).
25

Example 11

1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-[(phenylsulfinyl)methyl]-4- piperidinol, methane sulfonic acid salt

A solution of lithium bis(trimethylsilyl)amide (4ml, 1M in tetrahydrofuran) at -70° was treated with a solution of methylphenylsulfoxide (561mg) in tetrahydrofuran (2ml). After stirring for 10 mins the reaction was treated with a solution of 1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-piperidone (260mg) in tetrahydrofuran (2ml). The mixture was warmed to 20°C. After stirring for 1h the reaction was quenched with water (30ml) and extracted with ethyl acetate (50ml). The organic phase was washed with brine (30ml), dried and the solvent removed in vacuo to give a viscous oil. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (9:1) the appropriate fractions were bulked and the solvent removed in vacuo to give a white solid. This was redissolved in tetrahydrofuran (8ml) and treated with methane sulfonic acid (1.1mol equivalents), diluted with diethyl ether to give an off-white solid. This was collected by filtration to give the title compound (267mg). IR (Nujol) values include 3269, 1468, 1461, 1444, 1211, 1167, 1042 cm⁻¹. High- resolution FABMS calcd 401.1699, found 401.1695.

15

Example 12

(R)-1-[2-(5-Fluoro-1H-indol-3-yl)-ethyl]-4-(((2-methyl) phenylsulfinyl) methyl)-4-piperidinol

A solution of lithium bis(trimethylsilyl)amide (2ml, 1M in tetrahydrofuran) at -70° was treated with a solution of R(+) methyl(2-methyl)phenylsulfoxide (308mg) in tetrahydrofuran (2ml). After stirring for 5 mins the reaction was treated with a solution of 1-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-4-piperidone (130mg) in tetrahydrofuran (1ml). The mixture was warmed to 20°. After stirring for 30 mins the reaction was quenched with water (20ml) and extracted with ethyl acetate (50ml). The organic phase was washed with brine (30ml), dried and the solvent removed in vacuo to give a clear gum. This was purified by column chromatography on silica (Merck 7734) eluting with chloroform:methanol (9:1) the appropriate fractions were bulked and the solvent removed in vacuo to give the title compound (184mg) as a white foam. IR (CHBr₃) values include 3466, 1484, 1454, 759cm⁻¹. ¹H NMR (250MHz, CDCl₃) δ , 7.95-8.1 (2H,m,complex), 7.35-7.55 (2H,m,complex), 7.2-7.35 (m,complex,obscured by solvent), 7.1 (1H,m), 6.95

(1H,t J=9Hz,d J=2Hz), 4.12 (1H,s), 2.6-3.05 (10H,m,complex), 2.35 (3H,s), 2.05- 2.33 (2H,m,complex), 1.7-1.85 (2H,m,complex)ppm.CD λ_{max} (H₂O) 213nm ($\Delta\epsilon$ -17.70), 239 nm ($\Delta\epsilon$ -23.40)

5 Biological Data

The anxiolytic activity of the test compounds (\pm)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl]benzamide [(\pm) SR48968] and

Example 10, (R)-1-[2-(5-Fluoro- 1H-indol-3-yl) ethyl]- 4-[(phenylsulfinyl) methyl]-4-
10 piperidinol, methane sulphonic acid salt, was demonstrated in the mouse light-dark box and rat elevated plus- maze.

Mouse light-dark box:

15 The test was performed as described by Costall et al (see hereinbefore) in a box with black and white compartments illuminated by a 40W red and 40W white light, respectively. The time the mouse spent in the white side of the box during the 5min test period was determined. Results are expressed as percentage increase in time spent in the white side compared to vehicle treated control animals.

20

Results -

Example 10 100nmol/kg sc 30min pretreatment, 55% increase, $P < 0.05$

(\pm) SR48968 100 nmol/kg sc 30min pretreatment, 48% increase $P < 0.05$

25 Rat elevated plus-maze:

The test was performed as described by Handley and Mithani (see hereinbefore). The time the rat spent on the end halves of the open arms of the maze during the 3min test

30

period was determined. Results are expressed as percentage increase in time spent on the end halves of the open arms compared to vehicle treated control animals.

Results -

5 Example 10

100nmol/kg sc 30min pretreatment, 57% increase, $P < 0.05$

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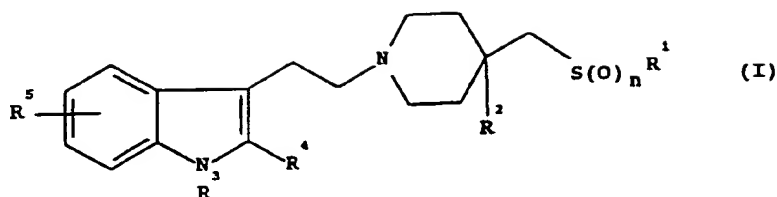
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CLAIMS

1. Compounds of formula (I)

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wherein

- 10 R^1 represents phenyl optionally substituted by one or two C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl groups or halogen atoms;
 R^2 represents hydrogen, hydroxy or C_{1-4} alkoxy;
 R^3 represents hydrogen or C_{1-4} alkyl;
 R^4 represents hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;
 15 R^5 represents hydrogen, a C_{1-4} alkyl, trifluoromethyl or cyano group, or a halogen atom;
 n represents zero, 1 or 2;
 and pharmaceutically acceptable salts thereof.

- 20 2. Compounds of formula (I) as claimed in Claim 1 wherein R^1 represents optionally substituted phenyl, n represents 1, R^2 represents hydroxy, R^3 represents hydrogen, R^4 represents hydrogen and R^5 represents a halogen atom.

3. A compound of formula (I) as claimed in Claim 1 or 2 selected from:

- 25 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylsulfinyl)methyl)-4-piperidinol;
 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((4-methyl)phenylsulfinyl)methyl)-4-piperidinol;
 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol;
 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-(((2-methyl)phenylthio)methyl)-4-piperidinol;
 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylthio)methyl]-4-piperidinol;
 30 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfonyl)methyl]-4-piperidinol;

1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[[[(2-methyl)phenylsulfonyl)methyl]-4-piperidinol;

4. A compound of formula (I) as claimed in any of Claims 1 to 3 for use in therapy.

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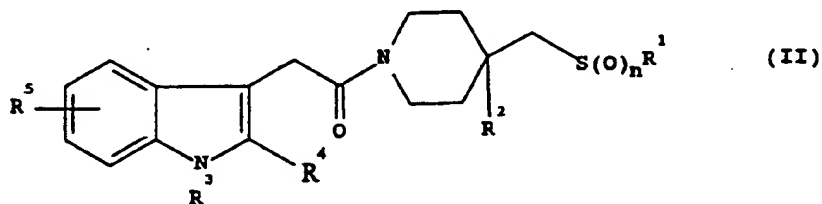
5. A method for the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK_2 receptor, comprising administration of an effective amount of a compound of formula (I) as claimed in any of Claims 1 to 3.

10 6. The use of a compound of formula (I) as claimed in any of Claims 1 to 3 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including NKA, NKB and substance P, acting at the NK_2 receptor.

15 7. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of Claims 1 to 3 together with a pharmaceutically acceptable carrier.

8. A process for the preparation of a compound of formula (I) as claimed in Claim 1, which process comprises:-

20 (A) where n is zero or two, reduction of a compound of formula (II)



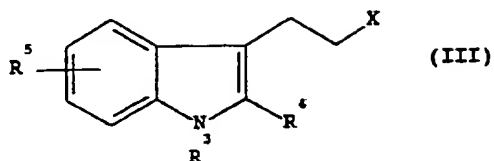
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wherein R^1 , R^2 , R^3 , R^4 , R^5 and n are as defined in Claim 1, using a suitable reducing agent;

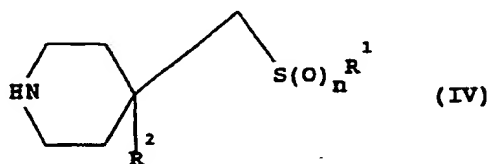
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B) reaction of a compound of formula (III)

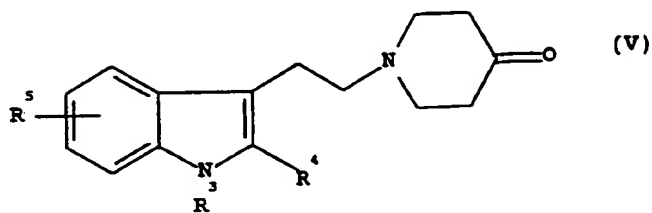


wherein X represents a suitable leaving atom or a group and R^3 , R^4 and R^5 are as defined in Claim 1, with a compound of formula (IV)

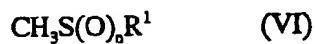


wherein R^1 , R^2 and n are as defined in Claim 1;

(C) where n is 1 or 2 and R^2 is hydroxy, reaction of a compound of formula (V)



where R^3 , R^4 and R^5 are as defined in Claim 1 with a compound of formula (VI)



where R^1 and n are as defined in Claim 1, after deprotection with a strong base; or

(D) converting a compound of formula (I) into another compound of formula (I).

9. The use of antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK_2 receptor, in the treatment of anxiety disorders.

5 10. The use of antagonists of tachykinins, including NKA, NKB and substance P, acting at the NK_2 receptor, in the preparation of a medicament for use in the treatment of anxiety disorders.

10 11. A method for the treatment of a mammal, including man, suffering from or susceptible to anxiety disorders, comprising administration of an effective amount of an antagonist of tachykinins, including NKA, NKB and substance p, acting at the NK_2 receptor.

12. The use or method according to any of Claims 9 to 11 wherein the tachykinin antagonist is
15 (S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butyl] benzamide or
(R)-1-[2-(5-Fluoro-1H-indol-3-yl) ethyl]- 4-[(phenylsulfinyl) methyl]-4-piperidinol;
or a pharmaceutically acceptable salt thereof.

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